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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/057,484	01/25/2002	Jackie R. See	47783/KMO/O194	4984

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EXAMINER	
KISHORE, GOLLAMUDI S	

ART UNIT	PAPER NUMBER
1615	9

DATE MAILED: 10/08/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
10/057,484	See
Examiner	**Art Unit**
Gollamudi S. Kishore, Ph.D	1615

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Jul 8, 2003* .

2a) ☒ This action is **FINAL.** 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-21 and 35-47* is/are pending in the application.

4a) Of the above, claim(s) *35-47* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-21* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 2
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

The request for the extension of time and amendment filed on 7-28-03 are acknowledged.

1. Newly submitted claims 35-47 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: The originally presented claims are product claims which could have been made by any process (for example mixing different populations of liposomes having the recited size ranges), whereas the newly added claims recite product claims made from a specific process.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 35-47 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Claims included in the prosecution are 1-21.

Double Patenting

2. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422

F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321© may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

3. Claims 1-21 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-7 and 15-34 of US 6,015,576. Although the conflicting claims are not identical, they are not patentably distinct from each other because instant generic claims include the specific volumes of the three different sizes of liposomes in the claims of said patent.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

4. Claims 1-21 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-7 and 14-31 of US 6,117,449. Although the conflicting claims are not identical, they are not patentably distinct from each other because instant generic 'antigens' includes the hepatitis C antigens in the claims of said patent.

5. Claims 1-21 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-51 of U.S. Patent No. 6,207,185. Although the conflicting claims are not identical, they are not patentably distinct from each

other because instant generic 'antigen' and 'size' include the specific antigens and specific sizes in terms of volumes, respectively recited in the claims of said patent.

Applicant indicates willingness to file terminal disclaimers once the allowableness of the claims is determined. The rejections are maintained in abeyance.

Claim Rejections - 35 U.S.C. § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> **A person shall be entitled to a patent unless --**
>
> **(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.**

7. Claims 1-2, 4-7, 15-18 and 20-21 are rejected under 35 U.S.C. 102(b) as being anticipated by Diminsky (New Generation of Vaccines, 1993).

Diminsky teaches lyophilized liposomes containing hepatitis antigen for use as a vaccine (note the abstract and Materials and Methods). Instant claims do not recite any percentages of specific populations of liposomes based on size. Therefore, the burden is upon applicant to show that the lyophilized liposomes are different from instant lyophilized liposomes.

Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant argues that the examiner has provided absolutely no factual or technical grounds to support that Diminsky's liposomes inherently have at least two sizes, before lyophilization. The following is the examiner's rationale for the inherency: on page 56, the reference teaches the average size of the liposomes is 4.5 microns. In order to obtain this average size, the Diminsky's larger liposomes must have at least this 4.5 micron upper limit. Furthermore, the methodology used by Diminisky as evident from page 56 involves a simple procedure of hydration of lipid film by salt solution leading to the formation of MLVs and the reference of Lichtenberg (cited of interest) shows that by this method the sizes of the liposomes formed are 0.5 microns to 10 microns (see the paragraph bridging pages 399 and 400). Therefore, it is the position of the examiner that the presence of three populations of liposomes having instant claimed sizes is inherent.

Claim Rejections - 35 U.S.C. § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> **(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.**

9. Claims 1-2, 4-7 and 10-21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sato (5,573,779) or Aramaki (Pharmaceutical Research, 1993) in view of Diminski

cited above by itself or in further in view of Gregoriadis (Liposomes as drug carriers, 1988).

Sato teaches oral liposomal vaccine formulations which reach Peyer's patches (note the abstract, columns 1-4, examples and claims). Sato however does not teach. Sato however, does not teach instant antigens. Sato also does not teach the lyophilization of the liposomes.

Similarly, Aramaki teaches the oral administration of antigens encapsulated in liposomes to be taken up by Peyer's patches (note the abstract, Materials and Methods, and discussion). Aramaki however, does not teach instant antigens. Aramaki also does not teach the lyophilization of the liposomes.

What is lacking in Sato, and Aramaki are the teachings of lyophilization of the liposomes and the use of specific claimed antigens.

Diminski as pointed above, teaches the use of liposomes containing hepatitis antigen in lyophilized form for use as a vaccine.

Gregoriadis while discussing the immunoadjuvant action of liposomes teaches that it is sometimes preferable that liposomes containing antigens be freeze-dried (note the entire article; in particular pages 282 and 286).

It would have been obvious to one of ordinary skill in the art to lyophilize the liposomes since both Diminski, and Gregoriadis teach that lyophilization is routinely practiced in the art and that it is sometimes preferable. In the absence of showing

unexpected results, it is deemed obvious to an artisan to use any antigen including claimed antigens in Sato's or Aramaki's teachings with the expectation of obtaining similar antibody response.

Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant argues that in making this rejection the examiner did not address the claim limitation requiring liposomes having at least two different sizes and that Diminsky or other references do not teach or suggest or inherently disclose the different sized liposomes of the present invention. This argument based on inherency has been addressed above.

Applicant argues that Sato does not teach or suggest the liposomal sizes; applicant argues that Sato states that the liposomes can be prepared by any suitable method and that liposomes having the desired sizes can be obtained by filtering the liposome solution. This might be true, but according to Sato on col. 3, line 62, the contents of the flask are subjected to a vortex or ultrasonic treatment. From this statement one can infer that Sato is teaching MLVs (by vortex treatment) and the secondary reference of Diminsky as discussed above, teaches the effectiveness of MLVs without fractionation. Therefore, even assuming that Sato's liposomes are fractionated to desired sizes, one of ordinary skill in the art would be motivated not to use a fractionation of the MLVs based on Diminsky's teachings. Applicant's arguments regarding Aramaki, and Gregoriadis once again pertain

to the lack of teachings of liposomes of claimed sizes; therefore, the same response as above, is applicable.

10. Claim 3 is rejected under 35 U.S.C. 103(a) as being unpatentable over Sato (5,573,779) or Aramaki (Pharmaceutical Research, 1993) in view of Diminski cited above by itself or in further in view of Gregoriadis (Liposomes as drug carriers, 1988), further in view of Geary (5,382,435).

The teachings of Sato, Aramaki, Diminski and Gregoriadis have been discussed above. What is lacking in these references is the teaching of enteric coating over the lyophilized preparations.

Geary teaches that Peyer's glands exist in the jejunum particularly in the lower portion thereof and in order to deliver acid and alkali labile agents to Peyer's patches the compositions have to be enterically coated. Geary's formulations include enteric coated liposome formulations for the delivery of pharmaceuticals including oral vaccines selectively to Peyer's patches. The composition is administered orally in the form of a capsule (note the abstract, col. 1, lines 35-39; col. 2, lines 36-68 and claim 6).

To use enterically coated capsules in the teachings of Sato, Aramaki. Diminsky and Gregoriadis would have been obvious to one of ordinary skill in the art since such enteric coating would enable the antigens in the compositions to reach Peyer's patches selectively.

Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant's arguments with regard to Sato, Aramaki, Diminski and

Gregoriadis have been addressed above. Applicant argues that Geary is not concerned with the sizes of the liposomes. It is true, but the reference is combined with the primary references for its teachings of or rationale for enteric coating of the preparations.

11. Claims 15 and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sato (5,573,779) or Aramaki (Pharmaceutical Research, 1993) in view of Diminski cited above by itself or in further in view of Gregoriadis (Liposomes as drug carriers, 1988), further in view of Fullerton (4,235,877).

The teachings of Sato, Aramaki, Diminski and Gregoriadis have been discussed above. What is lacking in these references is the teaching of the claimed specific antigens.

Fullerton while disclosing liposomal formulations containing bacterial and viral antigens teaches that liposomally encapsulated antigens are more active than free antigens. The antigens taught by Fullerton include hepatitis and influenza viruses (note the abstract, col. 2, line 21 et seq., and Examples).

The use of the antigens taught by Fullerton in the teachings of Sato, Aramaki, Diminski and Gregoriadis would have been obvious to one of ordinary skill in the art since Fullerton teaches that these antigens are more active in liposomes than free antigens.

Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant's arguments with regard to Sato, Aramaki, Diminski and Gregoriadis have been addressed above. Applicant argues that Fullerton is not concerned with the sizes of the liposomes. It is true, but the reference is combined with the primary

references for its teachings of enhanced activity of the encapsulated antigens compared to free antigens.

12. Claims 11 is rejected under 35 U.S.C. 103(a) as being unpatentable over Sato (5,573,779) or Aramaki (Pharmaceutical Research, 1993) in view of Diminski cited above by itself or in further in view of Gregoriadis (Liposomes as drug carriers, 1988), further in view of Barchfield (5,709,879).

The teachings of Sato, Aramaki, Diminski and Gregoriadis have been discussed above. What is lacking in these references is the teaching of HIV antigens.

Barchfield discloses high levels of immune response to liposomally encapsulated HIV antigens, gp120 and RT6(note the abstract and col. 7, lines 24-33).

The use of HIV antigens taught by Barchfield in the teachings of Sato, Aramaki, Diminski and Gregoriadis would have been obvious to one of ordinary skill in the art since Barchfield teaches higher levels of immune response by such an encapsulation.

Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant's arguments with regard to Sato, Aramaki, Diminski and Gregoriadis have been addressed above. Applicant argues that Barchfield does not teach two sizes of liposomes. It might be so, but the reference is combined with the primary references for its teachings of enhanced immune response of the encapsulated antigens compared to free antigens.

13. THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to *G.S. Kishore* whose telephone number is (703) 308-2440.

The examiner can normally be reached on Monday-Thursday from 6:30 A.M. to 4:00 P.M. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, T.K. Page, can be reached on (703)308-2927. The fax phone number for this Group is (703)305-3592.

Communications via Internet e-mail regarding this application, other than those under 35 U.S.C. 132 or which otherwise require a signature, may be used by the applicant and should be addressed to [thurman.page@uspto.gov].

All Internet e-mail communications will be made of record in the application file. PTO employees do not engage in Internet communications where there exists a possibility that sensitive information could be identified or exchanged unless the record includes a properly signed express waiver of the confidentiality requirements of 35 U.S.C. 122. This is more clearly set forth in the Interim Internet Usage Policy published in the Official Gazette of the Patent and Trademark on February 25, 1997 at 1195 OG 89.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703)308-1235.

Gollamudi S. Kishore, Ph. D

Primary Examiner

Group 1600

gsk

October 2, 2003